

Viral causes of psychiatric disease

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Summary

Current evidence on the role of viruses in the causation of psychiatric illness is reviewed. Herpes simplex encephalitis is relatively well defined but a wider role for this virus, particularly in relation to affective disorders, is suggested by some Scandinavian surveys of antibody titres in psychiatric populations. The extent to which influenzal illnesses and infectious mononucleosis may lead to neurotic, and occasional psychotic, episodes is the subject of controversy. The clinical literature is reviewed on the occurrence of encephalitis-like illnesses with prominent psychiatric and behavioural features. It is pointed out that no reliable criterion exists for differentiating these illnesses from such psychiatric syndromes as schizophrenia. It is suggested that neglect of this borderland area, and perhaps preconceptions concerning the features of 'organic' and 'functional' psychiatric disease, may have led to an underestimate of the possible role of viruses in the causation of psychiatric disease.

Introduction

In this paper an attempt is made briefly to review the evidence concerning the possible role of viral agents in the causation of psychiatric symptoms. The focus will be particularly upon the question of whether viruses may be the precipitant of illnesses whose only manifestation is in psychiatric symptoms, and the problem of whether viruses could contribute significantly to the aetiology of diseases, such as the functional psychoses, whose aetiology is at present obscure.

Recent interest in these questions stems particularly from the discovery of a transmissible agent in Creutzfeldt-Jakob disease, and the recognition that the nature of the infection in this case has unusual features, e.g. the lack of an antibody response; and also from the identification of the characteristics of slow virus infections of the nervous system such as subacute sclerosing panencephalitis and progressive multifocal leuco-encephalopathy. The spectrum of psychiatric disease to which a viral aetiology might conceivably be relevant is very wide, and may be said to extend at one end from herpes encephalitis, where the virus agent is identified and its role in the causation of specific symptoms is

relatively well established to, at the other end, the functional psychoses where a viral aetiology is speculative.

Herpes simplex

Drachman and Adams (1962) described the main features of herpes encephalitis as it is now recognized. They emphasized the relatively acute onset which is often associated with behavioural disturbance, fever, confusion, and changes referable to the temporal lobes, such as olfactory and gustatory hallucinations, anosmia, and memory loss. Histological changes are localized to the medial-temporal and orbital-frontal areas.

It is an open question as to whether there are cerebral manifestations of herpes simplex infections radically different in form from those seen in herpes encephalitis. Shearer and Finch (1964) reported the case of a 9-year-old boy who suffered over a 3-year period from seventeen separate episodes of organic psychosis, confusional in type, associated with recurrent herpes simplex labialis. Few, if any, similar cases have been reported. A quite different association of herpes virus with psychiatric disease is suggested by the work of Halonen *et al.* (1974) who, in a survey of 318 psychiatric patients, found type 1 herpes antibodies to be increased in patients with psychotic depression by comparison with other psychiatric patients, and healthy controls. Lycke, Norrby and Roos (1974) reported increased complement fixing antibodies to herpes virus in patients with depression, and to herpes virus and cytomegalovirus in patients with dementia. There was also a claim by Cleobury *et al.* (1971) that antibodies against herpes type 1 virus were significantly increased in aggressive psychopaths, by comparison with other psychiatric patients and a general hospital patient control group. However, the numbers of patients involved was small and these findings were not confirmed by Pokorny *et al.* (1973) who also found no increase in herpes virus antibodies in depressed patients. Therefore, the association of herpes virus with psychiatric illnesses other than herpes encephalitis remains obscure although the findings of Halonen *et al.* (1974) and Lycke *et al.* (1974) suggest the possibility of an association with some types of depression.

Psychiatric sequelae of common virus infections

In spite of the generally held view that such symptoms are common, the psychiatric sequelae of three common viral illnesses – influenza, infectious mononucleosis and infectious hepatitis – are still ill defined and the subject of controversy. Flewett and Hoult (1958) described two cerebral complications of influenza, an 'encephalopathy' associated with the acute attack and 'encephalitis' with an onset 3–14 days after such an attack, but were cautious about concluding that in either case there was a direct connection with the viral infection. The relationship of psychiatric symptoms to influenza infection is more tenuous. Menninger (1926) described a series of 200 post-influenzal psychoses following the 1918 epidemic and claimed that one third of these resembled dementia praecox. However, although many of these cases reported in detail are suggestive, the time relationship to influenza is highly variable. Moreover it is likely that many of these patients would not be given a diagnosis of schizophrenia by modern criteria. A series of nineteen cases of post-influenzal psychosis, of which a number were confusional, and seven had unusual olfactory hallucinations, was described from Barbados by Lloyd Still (1958). A case in which an acute confusional state followed by a persistent manic change developed in the course of a type A influenza illness was recently documented in detail by Steinberg *et al.* (1972). In none of these studies of psychotic illness has the virus been identified in CSF. In the realm of minor psychiatric illness Cluff, Canter and Imboden (1966) were able to demonstrate that post-influenzal symptoms were more likely to be reported by those who, on pre-illness questionnaire assessment, had been identified as psychologically vulnerable.

Infectious mononucleosis has a reputation for provoking depressive reactions but neither the frequency nor the mechanism have been systematically studied. Peszke and Mason (1969) were able to show that students who had suffered an attack of infectious mononucleosis were more likely subsequently to attend a university mental health clinic, and did so with lower pre-illness scores on the mental health section of the Cornell Medical Inventory than those who had not had the disease. Cadie, Nye and Storey (1976) found that anxiety, depression and somatic symptoms (assessed on the Middlesex Hospital Questionnaire) in women occurred more frequently in the year following an attack of infectious mononucleosis than in a control population, but this finding did not hold in their sample of men. Both these reports are consistent with the view that infectious mononucleosis may directly precipitate some psychiatric symptoms.

More serious neurological and psychiatric re-

sponses are reported. Gautier-Smith (1965) estimated the incidence of neurological complications as 7.3% and Boughton (1970) found it as high as 13% in hospital admissions. In an epidemic of seventy-five cases, five were noted by Klaber and Lacey (1968) to present with acute psychotic reactions, two of which were schizophrenic in form. Psychotic illnesses with features resembling acute schizophrenia and occurring in close association with attacks of infectious mononucleosis have been reported in detail by other authors (Raymond and Williams, 1948; Rzewuska-Szatowska, 1972).

The contribution of viruses to the causation of the 'functional' psychoses

There are in the literature a number of reports of illnesses which the authors have described as encephalitic, and which have been presumed to be viral in causation, in which schizophrenic features have been observed. These reports raise interesting theoretical, including nosological, problems.

These problems were first posed by encephalitis lethargica. The frequency with which schizophrenic features were seen in both the acute and chronic stages of the disease were discussed by Jelliffe (1927) and Hendrick (1928) and schizophrenia-like illnesses in individual cases were described, amongst other authors, by McCowan and Cook (1928). Hendrick (1928) points out that without neurological signs a diagnosis of schizophrenia in some cases would have been seriously considered, and noted that 'cases without neurological signs are occasionally diagnosed schizophrenia when a specific test, were there one, would have demonstrated a truly encephalitic process'. Of course in encephalitis lethargica the agent was never identified.

In the years since encephalitis lethargica was epidemic a number of authors have described illnesses presumed to be encephalitic, in which mental symptoms were prominent. Weinstein, Linn and Kahn (1955) reported a series of six cases of psychosis, four of which followed an upper respiratory tract infection, and one infectious mononucleosis. Disorientation, neurological signs, seizures and CSF changes in various combinations were observed but behavioural changes, and catatonic and other psychotic features, described by these authors as schizophrenic, were also seen.

A somewhat similar series of ten cases of post-infectious psychosis was reported by Sobin and Ozer (1966), and these authors stressed that the pattern of behaviour 'in many ways could not be distinguished from that of schizophrenia'. Seizures, dyskinesias and pyrexia occurred in some patients and, although most recovered in two to three months, one patient progressed to a defect state with evidence of brain atrophy. In 1966 Hunter and Jones

reported six cases seen in a psychiatric unit in a 3-month period with progressive personality change with perplexity and paranoid developments, emotionality and impairment of memory and concentration. Ocular changes and other neurological signs, although variable over time, were noted in all these patients, and a raised CSF protein was found in three; one patient died and one progressed to a defect state. These authors suggest that an encephalitis lethargica-type illness may still occur, perhaps in a milder or attenuated form in which the clinical picture has come to be increasingly dominated by psychiatric manifestations. In a series of eight patients reported as suffering from 'subacute encephalitis', Himmelhoch *et al.* (1970) identified an upper respiratory illness at onset in three cases. In two of three cases who died, subacute inclusion encephalitis was found at post-mortem, and in the third there was evidence of a viral meningo-encephalitis.

In all these series of cases it is apparent that illnesses which present with prominent psychiatric, and particularly schizophrenic, features, but in which there is some suspicion of an encephalitic process, either from the presence at some stage of neurological signs, of pyrexia or of abnormal CSF findings, are not rare. Only in the two cases reported by Himmelhoch *et al.* (1970) to show subacute inclusion encephalitis at post-mortem was the nature of the process defined.

Although in many of these cases the presence of disorientation or clouding of consciousness would by conventional criteria have excluded a diagnosis of schizophrenia, such 'organic' symptoms may be absent. Misra and Hay (1971) reported three cases who presented to a psychiatric unit in the course of 9 months with characteristically schizophrenic symptoms in clear consciousness, but who later became pyrexial, and developed neurological signs, although the CSF showed no abnormalities. One patient, an 18-year-old boy, progressed to a state of post-encephalitic Parkinsonism, and another to a chronic schizophrenic defect state.

A number of questions are provoked by these reports. Firstly, how is schizophrenia to be defined? Is it to be defined, as is conventionally the case, by the absence of organic or neurological features? This seems unwise when we do not know the causation either of the schizophrenic illnesses or of the supposed encephalitic processes which may so closely resemble them. The one may be more relevant to the other than has been thought. Nor can it be suggested that absence of CSF changes can constitute a criterion. CSF changes were absent in Misra and Hay's (1971) cases, and, as Hunter, Jones and Malleon (1969) have shown, are much more frequently present in unselected psychiatric

patients than would be expected on the view that organic changes are unusual in such populations. The presence of neurological signs is also a doubtful criterion since their detection depends upon the expertise of the examiner, and detailed examination is often difficult in unco-operative psychotic patients.

Recently, attention has been drawn to the possible association of catatonia with inflammatory processes. Penn *et al.* (1972) describe the case of a man of 25 years who presented with auditory and visual hallucinations, progressed to show *flexibilitas cerea* and posturing, and died after 9 days, post-mortem showing evidence of 'lymphocytic meningo-encephalitis'. Raskin and Frank (1974) reported the case of a 20-year-old female who presented with bizarre behaviour, became stuporous, and then developed pyrexia and was found to have cells in her CSF. Three cases of acute psychosis in which pyrexia, neurological signs and CSF cellular changes subsequently developed were reported by Wilson (1976). In two, catatonic motor phenomena were prominent, and in one of these, herpes simplex was isolated from the throat and a rising antibody titre demonstrated. Cases of subacute sclerosing panencephalitis have been reported with catatonic features of speech (Koehler and Jakumeit, 1976) and tonic posturing (Scully and McNeely, 1974).

Discussion

Viruses have been generally discounted as making a significant contribution to the chronic psychiatric morbidity arising from schizophrenic and other psychoses. It seems that this view is a consequence of the belief that encephalitis is associated with organic type psychological changes, with gross neurological signs and with CSF changes. However, the literature reviewed suggests that encephalitic illnesses with psychological changes of non-organic type, often resembling schizophrenia, are not rare, and may or may not be associated with CSF changes. Moreover CSF changes in psychiatric patients (Hunter *et al.*, 1969) and organic psychological impairments and structural abnormalities in the brain in schizophrenia (Johnstone *et al.*, 1978) may be more frequent than has been thought. If one allows that neither the form of the psychological changes, nor the presence or absence of neurological signs of CSF abnormalities, provide a reliable criterion of demarcation, it seems possible that the area of overlap may be larger than has generally been held to be the case. Attention has recently been drawn to the geographically localized type of encephalitis which is seen in the Yakut Republic of the U.S.S.R. and which is described as 'Vilyuisk encephalitis'. This illness may occur in acute and chronic forms and repeated exacerbations of acute symptoms lead to progressive impairments. The

disease may take several forms amongst which meningo-encephalitis and amyotrophic lateral sclerosis are frequent but, according to Petrov (1970) a schizophrenia-like syndrome is also common, and this progresses to dementia. There are similarities to and some possible epidemiological associations of this illness with known slow virus diseases of the central nervous system. Perhaps this condition provides a model for further investigations of the role of viruses in chronic psychiatric disease.

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